

Cancer in the UK

The most common causes of cancer in the UK are as follows*

- 1) Breast
- 2) Lung
- 3) Colorectal
- 4) Prostate
- 5) Bladder
- 6) Non-Hodgkin's lymphoma
- 7) Melanoma
- 8) Stomach
- 9) Oesophagus
- 10) Pancreas

*excludes non-melanoma skin cancer

The most common causes of death from cancer in the UK are as follows:

- 1) Lung
- 2) Colorectal
- 3) Breast
- 4) Prostate
- 5) Pancreas
- 6) Oesophagus
- 7) Stomach
- 8) Bladder
- 9) Non-Hodgkin's lymphoma
- 10) Ovarian

VISIT...

LANZAROTE
Caliente.COM

Tumour suppressor genes

- Genes which normally control the cell cycle
- Loss of function results in an increased risk of cancer
- Both alleles **must be mutated** before cancer occurs

Examples

Gene	Associated cancers
p53	Common to many cancers, Li-Fraumeni syndrome
APC	Colorectal cancer
BRCA1	Breast and ovarian cancer
BRCA2	Breast and ovarian cancer
NF1	Neurofibromatosis
Rb	Retinoblastoma
WT1	Wilm's tumour
Multiple tumor suppressor 1 (MTS-1, p16)	Melanoma

Tumour suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

P53:

- p53 is a tumour suppressor gene located on chromosome 17p
- It is the **most commonly** mutated gene in breast, lung and colon cancer
- P53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired.
- It may also be a key regulator of apoptosis

Li-Fraumeni syndrome:

- a rare **autosomal dominant** disorder
- characterised by the early onset of a variety of cancers such as sarcomas and breast cancer
- It is caused by mutation in the p53 gene

Tumour markers

Tumour markers may be divided into:

- 1) monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- 2) tumour antigens
- 3) enzymes (alkaline phosphatase, neurone specific enolase)
- 4) hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity (**used for follow up not diagnosis**)

Monoclonal antibodies

Tumour marker	Association
CA 125	Ovarian cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	• Hepatocellular carcinoma, • Teratomas • Nonseminoma testicular tumor
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	• Melanoma, • Schwannomas
Bombesin	• Small cell lung carcinoma, • gastric cancer, • neuroblastoma

- Beta-HCG and AFP are used to monitor testicular cancer
- β -hCG concentrations may be elevated in **seminomatous** or **nonseminomatous** tumours,
- AFP is increased only with **nonseminomatous tumours**
- AFP by itself is useful in monitoring liver cancer.
- CEA is used to monitor colorectal and breast cancers
- CA125 is most commonly used to monitor ovarian cancer but can also be raised in endometrial, lung, breast and gastrointestinal cancers.

Lung cancer Referral:

The 2005 NICE cancer referral guidelines gave the following advice:

A) Consider **immediate** referral for patients with:

- 1) signs of **SVC obstruction**
(Swelling of the face/neck with fixed elevation of jugular venous pressure)
- 2) **stridor**

B) Refer **urgently** patients with:

- 1) **persistent haemoptysis** (in smokers or ex-smokers aged 40 years and older)
- 2) **a chest X-ray suggestive** of lung cancer
(Including pleural effusion and slowly resolving consolidation)
- 3) a normal chest X-ray where there is a **high suspicion** of lung cancer
- 4) a history of **asbestos exposure** and:
 - ⇒ recent onset of chest pain,
 - ⇒ shortness of breath or
 - ⇒ unexplained systemic symptoms where a chest x-ray indicates pleural effusion, pleural mass or any suspicious lung pathology

Refer **urgently for chest x-ray** for patients with any of the following:

A) **haemoptysis**

B) **unexplained or persistent** (longer than 3 weeks):

- 1) chest and/or shoulder pain,
- 2) dyspnoea,
- 3) cough,
- 4) weight loss,
- 5) chest signs,
- 6) hoarseness,
- 7) finger clubbing,
- 8) cervical or supraclavicular lymphadenopathy,
- 9) features suggestive of metastasis from a lung cancer
(For example, secondaries in the brain, bone, liver, skin)

C) underlying **chronic respiratory** problems with **unexplained changes** in existing symptoms

Lung cancer

Types:

- 1) squamous:----- 35%
- 2) adenocarcinoma:-- 30%
- 3) small (oat) cell:----- 15%
- 4) large cell:-----10%
- 5) other c. 5%

Other tumours:

• Bronchoalveolar cell carcinoma:

- ☒ not related to smoking,
- ☒ ++sputum,
- ☒ Classically presents with progressive breathlessness and the production of large amounts of sputum (**bronchorrhoea**)
- ☒ Almost a half of patients are diagnosed on routine CXR, usually demonstrating a **peripheral lesion**.
- ☒ Its name arises from its pattern of growth along the alveolar walls without actually destroying them.
- ☒ It is an **adenocarcinoma**.
- ☒ In those whose tumour is not resectable, prognosis is poor.

• bronchial adenoma:

- ☒ mostly carcinoid

Lung cancer risk factors:

- 1) Smoking: increases risk of lung ca by a **factor of 10**

Other factors:

- 2) asbestos - increases risk of lung ca by a **factor of 5**
- 3) arsenic
- 4) radon
- 5) nickel
- 6) chromate
- 7) aromatic hydrocarbon
- 8) cryptogenic fibrosing alveolitis (IPF)

Factors that are NOT related:

- coal dust

Smoking and asbestos are synergistic, i.e. a smoker with asbestos exposure has a 10×5 = **50 times** increased risk

Central lesions: small cell, squamous cell, Bronchial adenoma

Peripheral lesion: bronchoalveolar cell carcinoma, adenocarcinoma

Non-small cell Lung cancer

There are three main subtypes of non-small cell lung cancer:

A) Squamous cell cancer (35%)

- 1) typically **central** (cavitating lung lesion)
- 2) associated with **parathyroid hormone-related protein** (PTHrP) secretion → hypercalcaemia
- 3) **hyperthyroidism** due to ectopic TSH
- 4) strongly associated with finger **clubbing**
- 5) **hypertrophic pulmonary osteoarthropathy** (HPOA)

B) Adenocarcinoma (30%)

- 1) **most common type of lung cancer in non-smokers**, although the majority of patients who develop lung adenocarcinoma are smokers
- 2) typically **located on the lung periphery**
- 3) gynecomastia

C) Large cell lung carcinoma (10%)

Management of Non-small cell Lung cancer:

- 1) only 20% suitable for surgery
- 2) **Mediastinoscopy** performed prior to surgery as CT does not always show mediastinal lymph node involvement
- 3) curative or palliative **radiotherapy**
- 4) poor response to chemotherapy

Surgery contraindications:

- 1) assess general health
- 2) stage IIIb or IV (i.e. metastases present)
- 3) FEV1 < 1.5 litres is considered a general cut-off point*
- 4) malignant pleural effusion
- 5) tumour near hilum
- 6) vocal cord paralysis
- 7) SVC obstruction

* However if FEV1 < 1.5 for lobectomy or < 2.0 for pneumonectomy then some authorities advocate further lung function tests as operations may still go ahead based on the results

Small Cell Lung Cancer (15%)

Features:

- 1) usually **central**
- 2) arise from **APUD cells** (Amine Precursor Uptake Decarboxylase)
- 3) associated with ectopic **ADH**, **ACTH** secretion
 - ⇒ **ADH** → hyponatraemia
 - ⇒ **ACTH** → Cushing's syndrome
 - ⇒ **ACTH** secretion can cause:
 - ✓ bilateral adrenal hyperplasia,
 - ✓ the high levels of cortisol can lead to hypokalaemic alkalosis
- 4) **Lambert-Eaton syndrome**: antibodies to voltage gated calcium channels causing myasthenic like syndrome

*an acronym for

- Amine - high amine content
- Precursor Uptake - high uptake of amine precursors
- Decarboxylase - high content of the enzyme decarboxylase

Management:

- 1) usually metastatic disease by time of diagnosis
- 2) Patients with very early stage disease (**T1-2a, N0, M0**) are now considered for **surgery**. NICE support this approach in their 2011 guidelines
- 3) however, most patients with limited disease receive a **combination** of chemotherapy and radiotherapy
- 4) patients with more extensive disease are offered **palliative chemotherapy**



CT scan showing small cell lung cancer with multiple pulmonary nodules and extensive mediastinal nodal metastases.

- The brain is a frequent site of first relapse in patients after complete therapeutic response.
- Prophylactic cranial irradiation should therefore be considered for patients with SCLC who have a response to initial chemotherapy.
- Prophylactic cranial irradiation based on randomised clinical trials largely applied to patients with limited-stage SCLC has demonstrated a decrease in the risk of intracranial relapse from 40% to 20% and improved long term survival by approximately 5%.

Lung carcinoid (1%) **(Bronchial adenomas)**

- The vast majority of **bronchial adenomas** are carcinoid tumours, arise from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours
- Lung carcinoid accounts 1% of lung tumours and for 10% of carcinoid tumours.
- The term bronchial adenoma is being phased out.

Features:

- 1) typical age = 40-50 years
- 2) smoking not risk factor
- 3) slow growing: e.g. long history of cough, recurrent haemoptysis
- 4) often **centrally** located and not seen on CXR
- 5) '**cherry red ball**' often seen on bronchoscopy
- 6) carcinoid syndrome itself is **rare** (associated with liver metastases)

Management:

- 1) surgical resection
- 2) if no metastases then 90% survival at 5 years

Paraneoplastic features in Lung cancer

A) Squamous cell:

- parathyroid hormone-related protein (PTH-rp) secretion causing hypercalcaemia
- hyperthyroidism due to ectopic TSH
- hypertrophic pulmonary osteoarthropathy (HPOA)
- clubbing

B) Adenocarcinoma:

- Gynaecomastia

C) Small cell:

- ADH
- ACTH (Increased cortisol)- not typical, hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness are more common than buffalo hump etc
- Lambert-Eaton syndrome



Hypertrophic pulmonary osteoarthropathy is a proliferative periostitis involving that typically involves the long bones. It is often painful.

Laryngeal cancer

- Initial therapy for stages I and II is radiation therapy or surgery.
- External beam radiation is the curative and function sparing treatment for this patient who has stage I and II laryngeal cancer.
- In the setting of lymph node-positive or locally advanced disease, the benefit of concurrent chemoradiotherapy is recommended.
- Cetuximab is a monoclonal antibody and is effective when combined with radiation, it has been found to improve local control and overall survival rates.

The TNM Classification of Malignant Tumours (TNM)

A cancer staging system that describes the extent of cancer in a patient's body

- T describes the size of the tumor and whether it has invaded nearby tissue,
- M describes distant metastasis (spread of cancer from one body part to another),
- N describes regional lymph nodes that are involved.

Primary Tumor (T)

TX	• Primary tumor cannot be assessed, or • tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	• Tumor 3 cm or less in greatest dimension, • surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): • involves main bronchus, 2 cm or more distal to the carina; • invades visceral pleura (PL1 or PL2); • associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 cm but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following : • parietal pleural (PL3), • chest wall (including superior sulcus tumors), • diaphragm, phrenic nerve, • mediastinal pleura, parietal pericardium; or

Tumor in the main bronchus less than 2 cm distal to the carina¹ but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

- T4** Tumor of **any size** that **invades any of the following**:
- mediastinum, heart, great vessels,
 - trachea, recurrent laryngeal nerve, esophagus,
 - vertebral body, carina,
 - separate tumor nodule(s) in a different ipsilateral lobe

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

- M1a**
- Separate tumor nodule(s) in a contralateral lobe,
 - tumor with pleural nodules or malignant pleural (or pericardial) effusion

M1b Distant metastasis (in extrathoracic organs)

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

- N3**
- Metastasis in contralateral mediastinal, contralateral hilar,
 - ipsilateral or contralateral scalene, or
 - supraclavicular lymph node(s)

Gastric cancer

Epidemiology:

- overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- peak age = 70-80 years
- more common in Japan, China, Finland and Colombia than the West
- more common in males, 2:1

Histology:

- **signet ring cells** may be seen in gastric cancer:
 - ✓ They contain a large vacuole of mucin which displays the nucleus to one side.
 - ✓ Higher numbers of signet ring cells are associated with a worse prognosis

Associations:

- 1) H. pylori infection
- 2) blood group A: gAstric cAnCer
- 3) gastric adenomatous polyps
- 4) pernicious anaemia
- 5) smoking
- 6) diet: salty, spicy, nitrates
- 7) may be negatively associated with duodenal ulcer

Investigation:

- 1) diagnosis: endoscopy with biopsy
- 2) staging:
 - CT or endoscopic ultrasound –
 - **endoscopic ultrasound** has recently been shown to be superior to CT

Hepatocellular carcinoma

- The third most common cause of cancer worldwide.
- Chronic hepatitis B is the most common cause of HCC worldwide with
- Chronic hepatitis C being the most common cause in Europe.
- The main risk factor for developing HCC is liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.

*Wilson's disease is an exception

Other risk factors include:

- 1) alpha-1 antitrypsin deficiency
- 2) hereditary tyrosinosis
- 3) glycogen storage disease
- 4) aflatoxin
- 5) drugs: oral contraceptive pill, anabolic steroids
- 6) porphyria cutanea tarda
- 7) male sex
- 8) diabetes mellitus, metabolic syndrome

Features:

- 1) tends to present late
- 2) features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- 3) possible presentation is decompensation in a patient with chronic liver disease

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol

Management options:

- 1) early disease: surgical resection
- 2) liver transplantation
- 3) radiofrequency ablation
- 4) transarterial chemoembolisation
- 5) sorafenib: a multikinase inhibitor

Colorectal cancer: see GIT

Prostate cancer

- Prostate cancer is now the most common cancer in **adult males** in the UK.
- The second most common cause of death due to cancer in **men** after lung cancer.
- The most common cause of **bone metastasis**

Risk factors:

- 1) increasing age
- 2) obesity
- 3) Afro-Caribbean ethnicity
- 4) **FH**: around 5-10% of cases have a strong family history

Features:

- Localised prostate cancer is **often asymptomatic**.
- This is partly because cancers tend to develop in the periphery of the prostate and hence don't cause obstructive symptoms early on.
- **Possible features include:**
 - 1) bladder outlet obstruction: hesitancy, urinary retention
 - 2) haematuria, haematospermia
 - 3) pain: back, perineal or testicular
 - 4) digital rectal examination:
 - ⇒ **asymmetrical, hard, nodular** enlargement with **loss of median sulcus**



Isotope bone scan (using technetium-99m labelled diphosphonates which accumulate in the bones) from a patient with metastatic prostate cancer. The scan demonstrates multiple, irregular, randomly distributed foci of high grade activity involving the spine, ribs, sternum, pelvic and femoral bones. The findings are in keeping with multiple osteoblastic metastases.

Metastatic bone disease from prostate cancer:

- Elevated serum prostate-specific antigen level is indicative of prostate cancer recurrence despite definitive treatment.
- If the patient is asymptomatic:
 - ⇒ Hormonal therapy with surgical castration **خصي** or
 - ⇒ gonadotropin hormone-releasing hormone (GnRH) agonists such as **leuprolide** is the treatment of choice.
- ☒ Patients may experience tumour-flare reactions with the use of GnRH agonists which cause a transient increase in testosterone, which can exacerbate prostate cancer symptoms.
- ☒ This can be prevented by:
 - ⇒ a brief course of concomitant antiandrogen therapy with agents such as **bicalutamide**, or **flutamide**
- Although **docetaxel-based chemotherapy** has been shown to improve survival this agent is generally indicated only for patients with **hormone-refractory cancer**.
- Median overall survival of patients with metastatic hormone-refractory prostate cancer is about 18 months.
- **Samarium-153** is a radionuclide useful in treating prostate cancer with painful bone metastases and is not useful when the patient is asymptomatic.

Bladder cancer

Risk factors

The following factors are associated with the development of bladder cancer:

- 1) **smoking**
- 2) occupational: **aniline dyes** used in **printing** and **textile industry** , صناعة الغزل والنسيج , **rubber** manufacture
- 3) **schistosomiasis**
- 4) drugs: **cyclophosphamide**

Testicular tumours

- The classical presentation for testicular tumours is that of a healthy male in the third or fourth decade of life with a painless, swollen, hard testis.
- Testicular cancer can be divided into germ cell and non-germ cell tumours.
 - 1) Germ cell tumours are classified as either:
 - ☒ pure seminomas or
 - ☒ mixed non-seminomatous germ cell tumours (NSGCTs):
These two groups comprise more than 90% of all tumours.
 - 2) Nongerm cell malignancies:
 - ☒ Leydig and Sertoli cell tumours, gonadoblastomas
 - ☒ make up less than 10% of all testicular tumours

Cryptorchidism:

- ☒ Patients with history of cryptorchidism have a 10- to 40-times increased risk of testicular cancer
- ☒ This risk is greater for the abdominal versus inguinal location of undescended testis.
- ☒ Orchidopexy does not reduce the risk of subsequently developing a malignancy.
- ☒ An abdominal testis is more likely to be seminoma
- ☒ A testis surgically brought to the scrotum by orchiopexy is more likely to be NSGCT.

Choriocarcinoma:

- The most aggressive of the NSGCTs.
- It disseminates haematogenously to lungs, liver, brain, bone, and other viscera very early in the disease process.
- Unlike classic seminoma or mixed GCTs, pure choriocarcinoma is more likely to present with symptoms from metastatic disease.
- Most testicular GCTs cause scrotal swelling, with a palpable mass, choriocarcinoma is different in that the local tumour may be small or nonpalpable.

Seminoma	Choriocarcinoma
☒ germ cell tumors ☒ Pure seminomas do not cause a rise in alpha-fetoprotein (AFP) level. ☒ (B-HCG) is only elevated in 10-15% of seminomas ☒ Gynecomastia rarely seen in patients with a seminoma ☒ On ultrasound scanning; Calcifications and cystic areas are less common in seminomas than in nonseminomatous tumours.	☒ non-seminomatous germ cell tumours ☒ Elevated AFP levels are most consistent with NSGCT, though AFP is often within the reference range in pure choriocarcinoma ☒ Beta-HCG is usually markedly elevated in pure choriocarcinoma ☒ Gynecomastia occurs due to elevation of beta-hCG levels and is therefore common in choriocarcinoma ☒ choriocarcinoma is associated with haemorrhage and necrosis and may appear more cystic, inhomogeneous, and calcified than a seminoma.

- **β -hCG (Beta-human chorionic gonadotropin) concentrations may be elevated in patients with seminomatous or nonseminomatous tumours,**
- **AFP is increased only in patients with nonseminomatous tumours.**
- **AFP is only produced by tumours containing embryonal and yolk sac elements**
- **Radical orchiectomy is required for definitive histologic staging and treatment, followed by additional staging studies such as a CT scan of the abdomen and pelvis and radiograph of the chest.**

Renal Cell Carcinoma

- Renal cell cancer is also known as hypernephroma
- Accounts for 85% of primary renal neoplasms.
- It arises from proximal renal tubular epithelium

Associations*

- 1) more common in middle-aged men
- 2) smoking
- 3) von Hippel-Lindau syndrome
- 4) tuberous sclerosis

*incidence of renal cell cancer is only slightly increased in patients with ADPKD

Features:

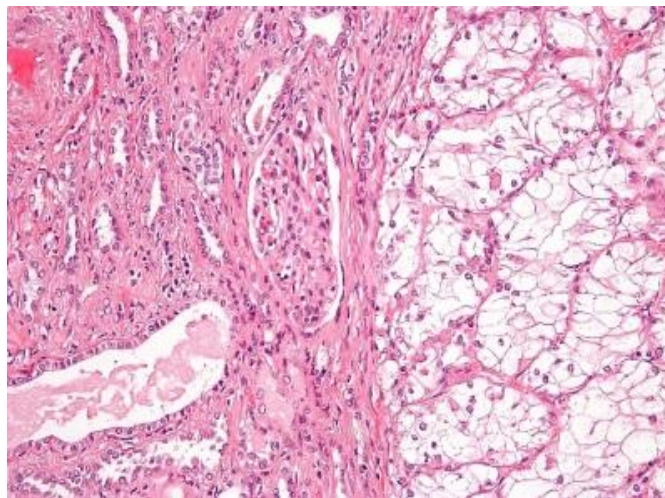
- 1) classical triad: haematuria, loin pain, abdominal mass
- 2) pyrexia of unknown origin FUO
- 3) left varicocele (due to occlusion of left testicular vein)
- 4) endocrine effects:
 - ⇒ may secrete erythropoietin (polycythaemia),
 - ⇒ renin,
 - ⇒ PTH (hypercalcaemia),
 - ⇒ ACTH
- 5) 25% have metastases at presentation

Management:

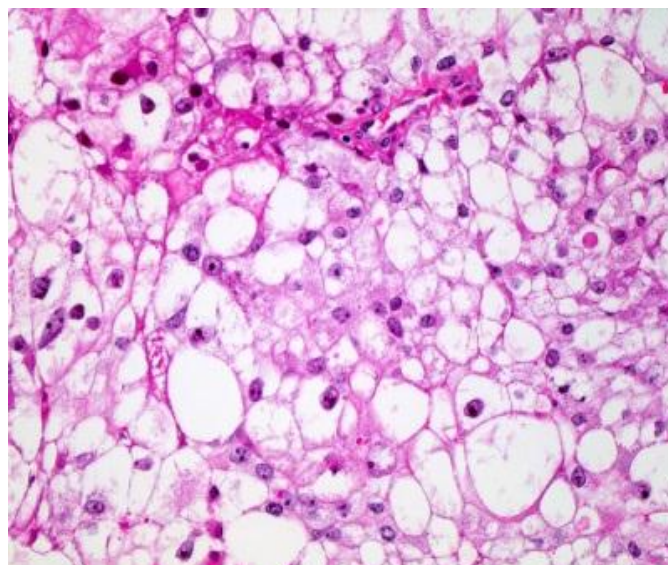
- 1) for confined disease a **partial or total nephrectomy** depending on the tumour size
 - 2) **alpha-interferon** and **interleukin-2** have been used to reduce tumour size and also treat patients with metastases
 - 3) **receptor tyrosine kinase inhibitors** (e.g. **sorafenib**, **sunitinib**) have been shown to have superior efficacy compared to interferon-alpha
- Sunitinib is one option for first line therapy in patients with advanced metastatic renal cell carcinoma which is incurable
 - Sunitinib is superior to interferon alfa in improving progression-free survival. (interferon alfa has significant toxicity).



Coronal CT scan of a middle-aged woman with renal cell cancer. Note the heterogeneously enhancing mass at the upper pole of the right kidney



Left: normal kidney. Right: 'clear-cell' pattern of renal cell carcinoma



'Clear-cell' pattern of renal cell carcinoma - clear cytoplasm, small nuclei

Wilms' tumour

- Wilms' nephroblastoma is one of the most common **childhood malignancies**.
- It typically presents in children under 5 years of age, with a median age of 3 years old

Features:

- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)

Associations:

- 1) hemihypertrophy
- 2) Beckwith-Wiedemann syndrome: an inherited condition associated with organomegaly, macroglossia, abdominal wall defects, Wilm's tumour and neonatal hypoglycaemia.
- 3) As part of WAGR syndrome with Aniridia, Genitourinary malformations, mental Retardation, also WT1 gene deletion.
- 4) one-third of cases are associated with a mutation in the WT1 gene on chromosome 11

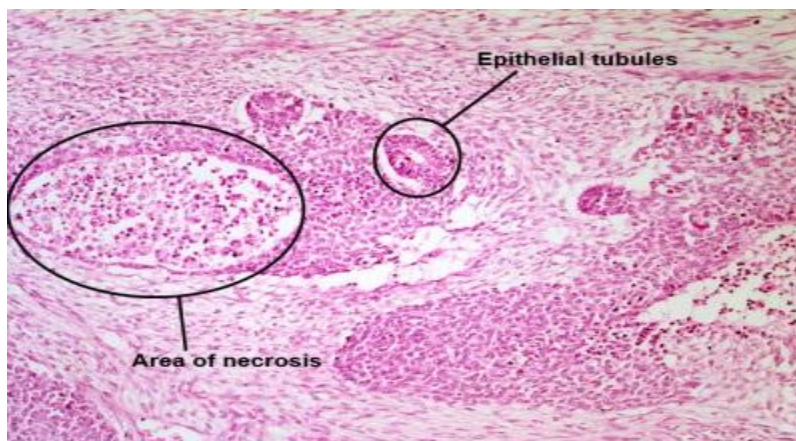
Aniridia (absence of the **iris**)

The G is sometimes instead given as "gonadoblastoma," since the genitourinary anomalies are tumours of the gonads (**testes** or **ovaries**).

(A subset of WAGR syndrome patients shows severe **childhood obesity**; the acronym WAGRO (O for **OBESITY**) used to describe this category)

Management:

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease
- prognosis: good, 80% cure rate



Histological features include epithelial tubules, areas of necrosis, immature glomerular structures, stroma with spindle cells and small cell blastomatous tissues resembling the metanephric blastema

Ovarian cancer

- Ovarian cancer is the fifth most common malignancy in females.
- The peak age of incidence is 60 years
- It generally carries a poor prognosis due to late diagnosis.
- Around 90% of ovarian cancers are epithelial in origin.
- HNPCC

Risk factors:

- 1) **family history:** mutations of the BRCA1 or the BRCA2 gene
 - 2) **many ovulations:** early menarche, late menopause, nulliparity
- It is traditionally taught that **infertility treatment** increases the risk of ovarian cancer, as it increases the number of ovulations. Recent evidence however suggests that there is not a significant link.
 - The combined oral contraceptive pill **reduces the risk** (fewer ovulations) as does having **many pregnancies**.

Clinical features: are **notoriously vague**:

- 1) abdominal distension and bloating
- 2) abdominal and pelvic pain
- 3) urinary symptoms e.g. Urgency
- 4) early satiety
- 5) diarrhoea

Diagnosis is difficult and usually involves diagnostic laparotomy

Management:

- 1) Patients with low risk, early-stage ovarian cancer
(Stage I, grade 1 disease confined to one or both ovaries with an **intact capsule** and **no ascites**)
⇒ After thorough surgical staging have a greater than 90% cure rate with **surgery alone** and close observation is required.
- 2) High risk, early-stage ovarian cancer
(Stage IC or II, grade 3 tumour or clear cell histology)
⇒ Platinum-based therapy, such as intravenous **carboplatin and paclitaxel**
- 3) Stage III disease: **Intraperitoneal chemotherapy**

Management of peritoneal carcinomatosis from ovarian cancer:

- ☒ **Debulking surgery** followed by **chemotherapy** is proven to be the best treatment in patients with peritoneal carcinomatosis from ovarian cancer.
- ☒ **Intraperitoneal chemotherapy** has less toxicity compared to IV chemotherapy and better tolerated.

Cervical cancer

- The incidence of cervical cancer peaks around the 6th decade.
- It may be divided into:
 - 1) Squamous cell cancer (80%)
 - 2) Adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Risk factors:

- 1) HPV 16,18 & 33
- 2) HIV
- 3) smoking
- 4) early first intercourse, many sexual partners
- 5) high parity
- 6) lower socioeconomic status
- 7) combined oral contraceptive pill**the strength of this association is sometimes debated

Breast Cancer

- Patients with **oestrogen receptor (ER)-positive tumours** are managed with:
 - ⇒ **endocrine therapy** with either **anastrozole** or **tamoxifen**
- Patients whose **tumours are ER-negative** or are **refractory to endocrine treatment**:
 - ⇒ Should receive **chemotherapy**
- Patients with **HER2 overexpression** warrant treatment with:
 - ⇒ **trastuzumab** in addition to
 - ⇒ **the chemotherapy**
- Several randomised trials have demonstrated that 52 weeks of adjuvant trastuzumab therapy reduces the risk for breast cancer recurrence in women with HER2 overexpression by approximately **50%** and may reduce mortality by as much as **30%**.
- Endocrine therapy such as tamoxifen or anastrozole is beneficial only in patients with ER-positive and progesterone receptor-positive tumours

Metastatic breast cancer

- Initial management of patients with **oestrogen receptor (ER)-positive** tumour status and metastatic breast cancer usually consists of serial endocrine therapies, including;
 - ⇒ **aromatase inhibitors**,
 - ⇒ **tamoxifen**,
 - ⇒ **fulvestrant** (an ER down-regulator), and
 - ⇒ **megestrol acetate**.
- Randomised trials support the use of an **aromatase inhibitor** (anastrozole, letrozole, or exemestane) as **first line** hormonal therapy for metastatic breast cancer in postmenopausal women as it is associated with superior response rates, time to progression, and overall survival compared with first line tamoxifen therapy.
- Chemotherapy is not indicated in the initial treatment of ER-positive metastatic disease because hormonal therapy is better tolerated and effective in producing an improvement in quality of life, although chemotherapy might be considered in patients with metastatic cancer with a large tumour burden in the vital organs for whom faster-acting chemotherapy might be life saving.
- In patients with bony metastases **hormonal therapy** is usually combined with **IV bisphosphonate** therapy; IV zoledronic acid monthly
- The evidence demonstrating benefit of oral bisphosphonate therapy such as alendronate in the treatment of bone metastases is conflicting.

Tamoxifen:

- Recommended for **first line** endocrine treatment of breast cancer in pre-menopausal women.
- It is both a partial agonist and antagonist of oestrogen.

Aromatase inhibitor (anastrozole & letrozole)

- first line hormonal therapy for metastatic breast cancer in postmenopausal women
- associated with superior response rates, time to progression and overall survival compared with first line tamoxifen therapy

Trastuzumab

- a monoclonal antibody directed against the **HER2/neu receptor**
- It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab.

Adverse effects

- 1) flu-like symptoms and diarrhoea are common
- 2) Cardiotoxicity:
 - ⇒ More common when **anthracyclines** have also been used.
 - ⇒ An echo is usually performed before starting treatment & regular follow up echo during treatment.

Bevacizumab:

- ⇒ Indicated only in patients with HER2-negative metastatic breast cancer

Fulvestrant: can be given parenterally

- A new novel therapy for endocrine treatment of metastatic breast cancer,
- It selectively **down regulates oestrogen receptors** and is equivalent to anastrozole in efficacy.
- Fulvestrant is the only endocrine agent currently available that can be given parenterally, which offers significant advantages to patients with swallowing difficulties.

(ER estrogen, PR progesterone)

Ductal carcinoma in situ (DCIS)

- The incidence of DCIS has been increasing because of widespread use of screening mammography.
- Local therapy with mastectomy or wide-excision **resection** and **radiation** therapy are indicated but not chemotherapy.
- Patients with DCIS are at increased risk for new or locally recurrent breast cancer in the contralateral or ipsilateral breast.
- In patients with **oestrogen receptor-positive tumours**, **tamoxifen therapy** for **5 years** in addition to **lumpectomy** decreases the risk of a new breast cancer event.
- Most patients treated with lumpectomy without radiation therapy have a high risk for local recurrence.
- **Sentinel lymph node biopsy** is safe and adequate for screening the axillary lymph nodes for metastases in women with small breast tumours.

Breast-conserving therapy:

- ☒ generally indicated for patients with focal disease
- ☒ randomised clinical trials have shown that the survival rate for women undergoing breast-conserving therapy is equivalent to that of those who undergo mastectomy
- ☒ Improved cosmetic outcomes and less morbidity than mastectomy.
- Adjuvant chemotherapy offers no proven benefit in patients with DCIS.
- **Mastectomy would be indicated in:**
 - 1) patients in whom complete excision cannot be achieved unless mastectomy is performed or
 - 2) radiation is contraindicated
- Prophylactic mastectomy is indicated only in patients with BRCA1 or BRCA2.
- **Raloxifene** is indicated only for **primary prevention** of breast cancer in postmenopausal women and is not used to treat DCIS.

Thyroid Cancer

Features of hyperthyroidism or hypothyroidism are **not commonly** seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

PFMAL

Type	Percentage	
Papillary	70%	• Often young females • excellent prognosis
Follicular	20%	
Medullary	5%	• Cancer of parafollicular cells, • secrete calcitonin, • part of MEN-2
Anaplastic	1%	• Not responsive to treatment(palliative TTT), • can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Papillary and follicular cancer

Management:

- 1) **total thyroidectomy**
- 2) Followed by **radioiodine** (I-131) to kill the normal thyroid tissue remnants and microscopic foci of residual tumour.
- 3) yearly **thyroglobulin** levels to detect early recurrent disease

Medullary thyroid tumours

- Do not concentrate radioiodine and must be treated with **thyroidectomy**.
- Metastatic or recurrent disease is treated with **chemotherapy or radiotherapy**.
- Because it is caused by C cell proliferation which are not TSH-responsive, levothyroxine is not effective in treatment

Anaplastic thyroid cancer - aggressive, difficult to treat and often causes pressure symptoms

- ☒ There is no evidence that radiation therapy prolongs life, although it is used if patients have pressure symptoms from the neck mass in anaplastic thyroid cancer.
- ☒ There is no role for the routine adjuvant chemotherapy in patients with differentiated thyroid cancer.

Follicular thyroid carcinoma (FTC)

- A well-differentiated tumour. FTC resembles the normal microscopic pattern of the thyroid.
- FTC originates in follicular cells and is the second most common cancer of the thyroid after papillary carcinoma.
- The most common presentation of thyroid cancer is an asymptomatic thyroid mass, or a nodule, that can be felt in the neck.
- The staging of well-differentiated thyroid cancers is related to age for the first and second stages but not related for the third and fourth stages.

Younger than 45 years:

- 1) Stage I - Any T, any N, M0 (Cancer is in the thyroid only).
- 2) Stage II - Any T, any N, M1 (Cancer has spread to distant organs).

Older than 45 years:

- 1) Stage I - T1, N0, M0 (Cancer is in the thyroid only and may be found in one or both lobes).
 - 2) Stage II - T2, N0, M0 and T3, N0, M0 (Cancer is in the thyroid only and is larger than 1.5 cm).
 - 3) Stage III - T4, N0, M0 and any T, N1, M0 (Cancer has spread outside the thyroid but not outside of the neck).
 - 4) Stage IV - Any T, any N, M1 (Cancer has spread to other parts of the body).
-
- Surgery is the definitive management of thyroid cancer. Various types of operations may be performed.
 - Lobectomy with isthmectomy is the minimal operation for a potentially malignant thyroid nodule.
 - Patients less than 40 years who have FTC nodules less than 1 cm, well defined, minimally invasive, and isolated may be treated with hemithyroidectomy and isthmectomy.
 - If feasible, subtotal thyroidectomy (small part of contralateral lobe retained) is preferable since it carries a lower incidence of complications (for example, hypoparathyroidism, superior and/or recurrent laryngeal nerve injury).
 - Approximately 10% of patients who have had total thyroidectomy (removal of all thyroid tissue preserving the contralateral parathyroid glands) demonstrate cancer in the contralateral lobe.
 - Total thyroidectomy should be performed in patients who are more than 40 years with FTC and in any patient with bilateral disease.
 - Total thyroidectomy is recommended for any patient with a thyroid nodule and a history of irradiation.

- Some studies show lower recurrence rates and increased survival rates in patients who have undergone total thyroidectomy. This surgical procedure also facilitates earlier detection and treatment of recurrent or metastatic carcinoma.
- Patients receive radioiodine four to six weeks after thyroidectomy to detect and destroy any metastases and any residual tissue in the thyroid.
- Following thyroidectomy, patients will need to take **thyroid replacement therapy**.
- External beam radiation is used in the management of FTC if the cancer cannot be resected, or if there is extension into adjacent structures. Radiotherapy may also be administered postoperatively to reduce the risk of local-regional recurrence. It may also be used palliatively to treat pain from bone metastases.
- Chemotherapy with cisplatin or doxorubicin has limited efficacy. It may be employed when other treatment modalities have failed.

Thymoma

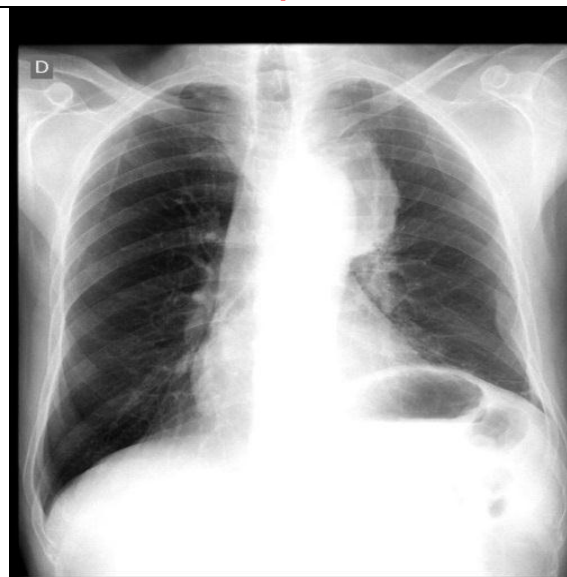
- Thymomas are the most common tumour of the anterior mediastinum
- Usually detected between the sixth and seventh decades of life.

Associated with:

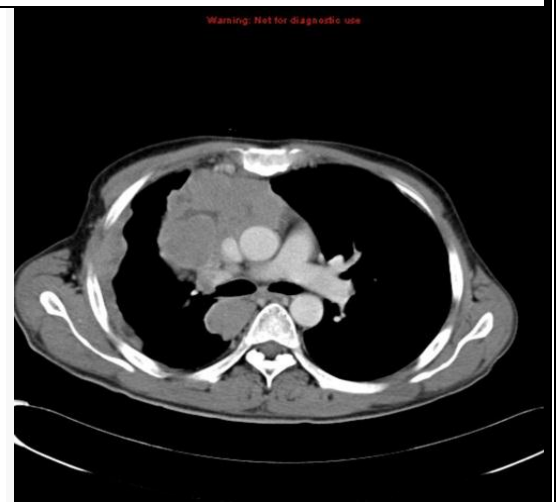
- 1) **myasthenia gravis** (30-40% of patients with thymoma)
- 2) **red cell aplasia**
- 3) dermatomyositis
- 4) also : SLE, SIADH

Causes of death:

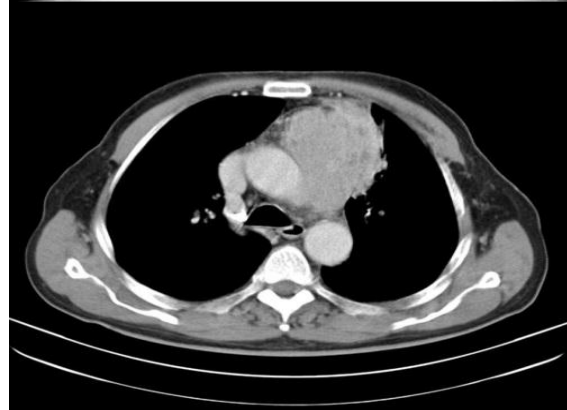
- 1) airway compression
- 2) **cardiac tamponade**



Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour.



CT slice at the bifurcation of the main bronchus showing an invasive thymoma presenting as an anterior mediastinal mass



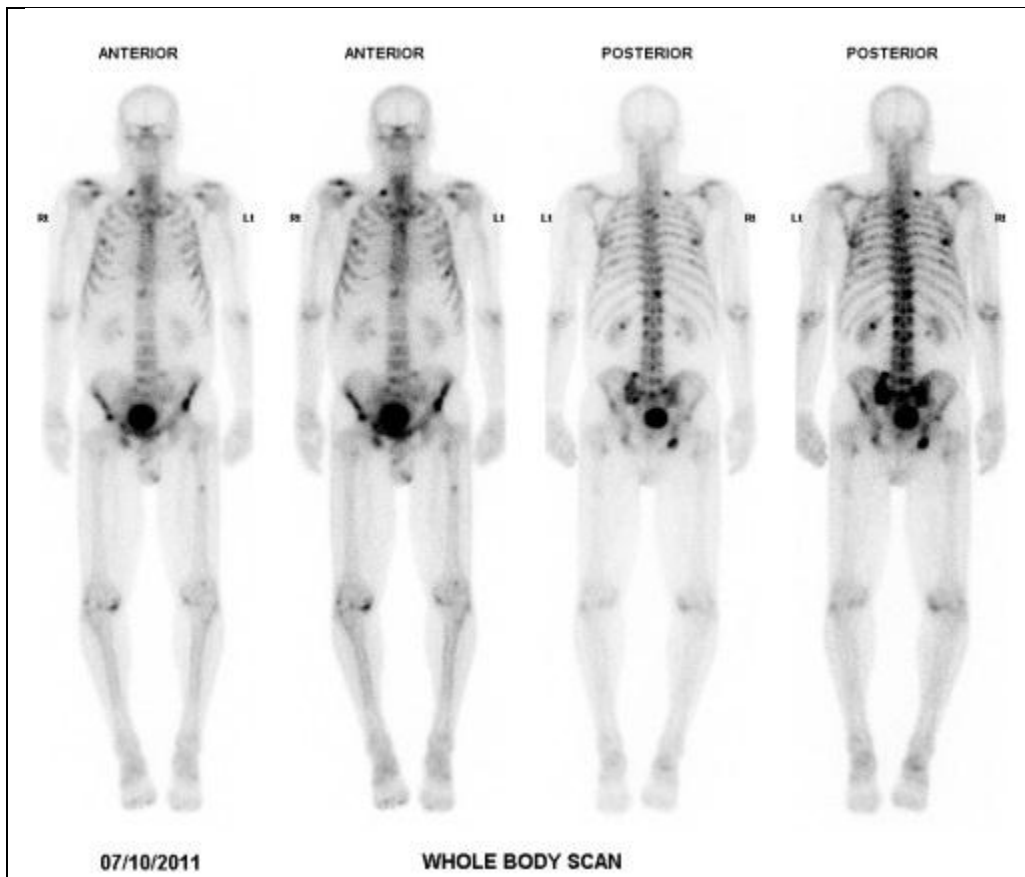
Bone metastases

Most common tumour causing bone metastases (in descending order)

- 1) **prostate**
- 2) **breast**
- 3) **lung**

Most common site (in descending order)

- 1) **spine**
- 2) **pelvis**
- 3) **ribs**
- 4) **skull**
- 5) **long bones**



Isotope bone scan (using technetium-99m labelled diphosphonates which accumulate in the bones) from a patient with metastatic prostate cancer. The scan demonstrates multiple, irregular, randomly distributed foci of high grade activity involving the spine, ribs, sternum, pelvic and femoral bones. The findings are in keeping with multiple osteoblastic metastasis.

Spinal cord compression

- Spinal cord compression is an **oncological emergency**
- Affects up to 5% of cancer patients.
- Extradural compression accounts for the majority of cases, usually due to **vertebral body metastases**.
- It is more common in patients with **lung, breast and prostate** cancer

Features:

- 1) **back pain:**
 - The earliest and most common symptom
 - may be worse on lying down and coughing
- 2) lower limb weakness
- 3) sensory changes: sensory loss and numbness
- 4) **neurological signs** depend on the level of the lesion:
 - 1) Lesions above **L1** usually result in:
 - UMN signs in the legs and a sensory level.
 - 2) Lesions below **L1** usually cause:
 - LMN signs in the legs and perianal numbness.
 - 3) Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion

Management:

- 1) **high-dose oral dexamethasone** (**dexamethasone 8 mg BD PO**) , **MRI all spines within 24 hrs then**
- 2) **urgent oncological** assessment for consideration of radiotherapy or surgery
- 3) **Below L1** is arranged urgently, rather than immediately. **Immediate** radiotherapy is necessary for lesions **above L1**.

- Spinal cord compression occurs in 5% of all cancer patients and 10% of those with spinal metastases.
- The most common site is the thoracic spine (~70%), followed by lumbar spine (~20%).
- Dexamethasone 16 mg od and omeprazole 20 mg od is correct
- A proton pump inhibitor such as omeprazole or lansoprazole should be added as gastric protection whilst remaining on the course of steroids.
- The steroids should be started as soon as the diagnosis is considered, unless contraindicated or lymphoma is suspected.
- If the diagnosis of metastatic spinal cord compression is confirmed the steroids should be continued at high dose for five to seven days and then slowly reduced.

Dexamethasone given for spinal cord compression can be given via any available route. Giving it intravenously offers no significant advantage over giving it orally.

16 mg dexamethasone should be offered to all patients with MSCC as soon as possible after assessment. There are only a few contraindications to this, including a

significant suspicion of lymphoma. The possibility of spinal surgery does not influence the prescribing of corticosteroids in this situation.

Spinal stabilisation surgery should be urgently considered for:

- Patients with spinal metastases and imaging evidence of structural spinal failure with spinal instability and
- Patients with spinal metastases and mechanical pain resistant to conventional analgesia, even if they have been completely paralysed for more than 24 hours.

Preoperative radiotherapy should not be carried out although postoperative fractionated radiotherapy can be offered to patients with a satisfactory outcome, once the wound has healed.

Patients should be assessed at least once a day for changes in bowel and bladder function. Bladder dysfunction should be managed with a urinary catheter on free drainage although this should not be performed automatically on all MSCC patients.

Superior vena cava obstruction (SVCO) from lung cancer needing urgent treatment;

The best initial treatment is with **high dose steroids**.

CT chest then

Stenting or radiotherapy to his SVC

Hormone replacement therapy

See pharmacology

Monoclonal antibodies

- Monoclonal antibodies have an increasing role in medicine.
- They are manufactured by a technique called **somatic cell hybridization**.
- This involves the fusion of **myeloma cells** with **spleen cells** from a mouse that has been **immunized** with the desired **antigen**.
- The resulting fused cells are termed a **hybridoma** and act as a 'factory' for producing monoclonal antibodies.
- The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (**HAMAs**).
- This problem is overcome by combining the variable region from the mouse antibody with the constant region from a human antibody.

Monoclonal Antibodies	used in
Infliximab (Anti-Tnf)	1) rheumatoid arthritis and 2) Crohn's
Rituximab (Anti-Cd20)	1) rheumatoid arthritis 2) non-Hodgkin's lymphoma
Cetuximab (Epidermal Growth Factor Receptor Antagonist)	1) metastatic colorectal cancer tumour express K-Ras 2) head and neck cancer
Trastuzumab (Her2/Neu Receptor Antagonist)	metastatic breast cancer
Alemtuzumab (Anti-Cd52)	CLL
Abciximab (Glycoprotein IIb/IIIa Receptor Antagonist)	prevention of ischaemic events in patients undergoing PCI
Okt3 (Anti-Cd3)	prevent organ rejection

Monoclonal antibodies are also used for:

- 1) medical imaging when combined with a radioisotope
 - 2) identification of cell surface markers in biopsied tissue
 - 3) diagnosis of viral infections
- **Cetuximab** works by blocking the extracellular domain of EGFR preventing ligand binding and therefore preventing downstream signal transduction.
 - The patient's tumour must express **K-Ras wild type** as K-Ras mutated is constitutively active regardless of whether a ligand is attached or not.
 - Cetuximab is licensed by NICE in metastatic colorectal cancer for K-Ras wild type proven patients who require downstaging prior to surgical resection of liver metastatic disease.
 - This is always given in combination with chemotherapy and causes an acne type rash as its major side effect.

Cytotoxic agents

See pharmacology

Tumour lysis syndrome

- Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high grade lymphomas and leukaemias.
- It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy.
- On occasion it can occur with steroid treatment alone.
- Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.
- Patients at high risk of TLS should be given **IV allopurinol** or **IV rasburicase** immediately prior to and during the first days of chemotherapy.
- **Rasburicase** is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin.
- Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys.
- Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.
- TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell.
- It leads to:
 - 1) high uric acid level
 - 2) High potassium
 - 3) high phosphate
 - 4) **Low** calcium.
- It should be suspected in any patient presenting with an **AKI** in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system:

A) Laboratory tumor lysis syndrome:

Abnormality in two or more of the following, occurring within **3** days before or **7** days after chemotherapy:

- 1) uric acid > 475 $\mu\text{mol/l}$ or 25% increase
- 2) potassium > 6 mmol/l or 25% increase
- 3) phosphate > 1.125 mmol/l or 25% increase
- 4) calcium < 1.75 mmol/l or 25% decrease

B) Clinical tumor lysis syndrome:

Laboratory tumor lysis syndrome **plus one** or more of the following:

- 1) increased **serum creatinine** (1.5 times upper limit of normal)
- 2) **seizure**
- 3) **cardiac arrhythmia** or
- 4) **sudden death**

Palliative care prescribing

Agitation and confusion

- Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication.
- If specific treatments fail then the following may be tried:
 - 1) **first choice:** haloperidol
 - 2) other options: chlorpromazine, levomepromazine
- ☒ In the terminal phase of the illness then agitation or restlessness is best treated with midazolam (dormicum)

Hiccups

Management of hiccups:

- 1) chlorpromazine ([typical anti-psychotic](#)) is licensed for treatment of intractable hiccups
- 2) haloperidol, gabapentin are also used
- 3) dexamethasone is also used, particularly if there are hepatic lesions

Haematuria

- If a patient is having a large bleed (for example is haemodynamically unstable) then admission may be appropriate, depending on individual circumstances
- For non-life threatening bleeds
 - 1) encourage increased **fluid intake** to prevent clot retention
 - 2) exclude **urinary tract infection**
 - 3) **etamsylate 500mg qds** may decrease bleeding*
 - 4) consider referral for **palliative radiotherapy**

*tranexamic acid is generally **avoided** as it may promote the formation of hard clots which cannot be passed

Palliative care prescribing for pain

NICE guidelines In 2012 NICE published guidelines on the use of opioids in palliative care.

Starting treatment:

- 1) when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release **morphine** (depending on patient preference), with oral immediate-release morphine for breakthrough pain
- 2) If no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required
- 3) oral modified-release morphine should be used in preference to transdermal patches
- 4) laxatives should be prescribed for all patients initiating strong opioids
- 5) Patients should be advised that nausea is often **transient**. If it persists then an antiemetic should be offered
- 6) drowsiness is usually **transient** - if it does not settle then adjustment of the dose should be considered

SIGN guidelines SIGN issued guidance on the control of pain with cancer in 2008. Selected points:

- 1) the breakthrough dose of morphine is one-sixth the daily dose of morphine
- 2) all patients who receive opioids should be prescribed a laxative
- 3) Opioids should be used with caution in patients with CKD.
- 4) **fentanyl**, **Alfentanil** and **buprenorphine** are preferred in patients with CKD
- 5) metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy
- 6) When increasing the dose of opioids the next dose should be increased by 30-50%.

Opioid side-effects

Usually transient	Usually persistent
Nausea Drowsiness	Constipation

Opiate induced nausea:

- **Haloperidol** is the first choice antiemetic for opiate induced nausea in the palliative care setting.
- Haloperidol acts as a central dopamine antagonist. The chemoreceptor trigger zone (CTZ) is rich in dopaminergic receptors. Opioid related nausea is thought to be predominantly due to dopamine pathways in the CTZ.
- Domperidone and metochlopramide also have central antidopaminergic activity but less than haloperidol and therefore not as effective (much of their antiemetic action is due to their peripheral effects on the gut).
- Levomepromazine has several mechanisms of action and can be used for opiate induced nausea but is not as effective as haloperidol. The same goes for cyclizine.

Constipation

- ☒ Constipation is common in patients with advanced cancer, particularly in those taking opioid medication, with reduced oral intake and reduced mobility.
- ☒ **Polyethylene glycol** (Movicol) would seem the best choice in this scenario. It has an osmotic action and helps to retain water in the gut to aid faecal passage. It is generally better tolerated than some other oral laxatives and has been shown to be more effective than lactulose in the management of chronic constipation.
- ☒ Lactulose (an osmotic laxative) is usually avoided in palliative care as it can cause abdominal cramps and excessive flatulence. Its sweet taste can be unpalatable for some patients and it needs to be consumed with large volumes of liquid which is sometimes not practical for palliative care patients.

Morphine toxicity

- The rarer symptoms of neurotoxicity (for example, **hallucinations**, **myoclonus** and **delirium**) and **respiratory depression** are the cause of much anxiety amongst prescribers.
- Pain acts as a psychological antagonist to the respiratory depressant effect of morphine which means that naloxone is rarely needed in palliative care.

1 Morphine	= 10 codeine = 10 tramadol
1 oxycodone	= 2 Morphine
transdermal fentanyl	= 2.5 morphine
transdermal buprenorphine	
1 diamorphine	= 3 Morphine

Conversion between opioids

From	To	Conversion factor
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 10

Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

From	To	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2**

The current BNF gives the following conversion factors for transdermal preparations

- 1) transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily
- 2) transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily

From	To	Conversion factor
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

**historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

- ✗ Fentanyl transdermal patch 25 micrograms per hour changed every 72 hours is equivalent to 60 to 130 mg of morphine per 24 hours, and
- ✗ Transdermal fentanyl would not be appropriate in acute setting; steady state will only be obtained > 24 hours post-application. Toxicity is difficult to manage as patches have a very long half life.
- ✗ **SC fentanyl** is used for the treatment of acute pain in renal patients.
- Oxycodone By mouth it is more potent than morphine and, although studies suggest differing conversions, a potency ratio of 2:1 (oxycodone to morphine) is generally employed.
- As oxycodone is more expensive than morphine, it should be reserved for those patients unable to tolerate morphine.
- In order to convert an oral dose of oxycodone to a 24 hour subcutaneous syringe driver you must first calculate the total daily oral dose (that is, in this case $30 + 30 = 60$ mg).
- Then, to convert this to a 24 hour subcutaneous route you must divide by two (that is, $60 / 2 = 30$ mg).

- The conversion for oral morphine to subcutaneous diamorphine is one third. So 20 mg MST bd is a total of 40 mg oral morphine in 24 hours and one third of this is 13.3 mg diamorphine. This can be rounded to 15 mg.

Standard practice would be to follow the World Health Organization recommendations for the management of cancer pain, which suggest analgesia should be given:

- By the mouth - that is, using the oral route for all drugs including morphine and other opioids unless patient is vomiting, semi-conscious, has dysphagia, etc.
- By the clock - persistent pain requires preventative treatment and as needed (prn) analgesia only is not acceptable.
- By the ladder - that is, the WHO analgesic ladder.

The WHO analgesic ladder is as follows:

- Step 1 ⇒ Non-opioid +/- adjuvants (e.g. paracetamol/NSAIDs)
- Step 2 ⇒ Weak opioid + non-opioid +/- adjuvants (e.g. co-codamol 30/500)
- Step 3 ⇒ Strong opioid + non-opioid +/- adjuvants (e.g. morphine, fentanyl, oxycodone).

Co-codamol (codeine 30 mg + paracetamol 500 mg)

Oramorph® (Immediate release morphine sulphate solution)

MST® (slow release morphine sulphate tablets)

If midazolam is not successful in controlling seizures in an end of life situation subcutaneous phenobarbitol can be used but this should be on the advice of specialists only.

NSAID in IHD ??

- A non-steroidal anti-inflammatory drug (NSAID) would seem a good treatment for this gentleman's bone pain but the choice is a difficult one given his history of ischaemic heart disease.
- Cyclo-oxygenase-2 (COX2) selective inhibitors (for example, celecoxib and rofecoxib) are associated with an increased risk of thrombotic events (for example, myocardial infarction and stroke) and are rarely used in preference to non-selective agents.
- COX2 selective inhibitors are, however, associated with a lower risk of serious upper GI side effects and can be a good choice for those with a high risk of ulceration or bleeding.
- Some non-selective NSAIDs are also associated with an elevated thrombotic risk, including diclofenac 150 mg daily and ibuprofen 2.4 g daily, therefore these are also the incorrect choices in this case.
- Naproxen (1 g daily) is associated with a lower thrombotic risk which makes it the correct answer in this case.
- Low dose ibuprofen (1.2 g daily) would also be a relatively safe choice for this patient as it has not been linked to an increased risk of myocardial infarction.
- Other considerations when prescribing NSAIDs are that they should be avoided in renal failure and used with caution in the elderly.
- All NSAIDs are contraindicated in severe cardiac failure and in those patients with a history of hypersensitivity to aspirin.
- They should be used with caution in those patients with coagulation defects and it is worth noting that long term use of NSAIDs can lead to impaired female fertility (reversible on withdrawal of the drug).

Palliation of breathlessness

- Breathlessness is a significant problem in the palliative care setting and not just in patients with lung cancer.
- Palliation of breathlessness involves use of opioids, other medications, physiotherapy and psychological support.
- **Opioids** are very effective agents to reduce the sensation of breathlessness - they reduce inappropriate respiratory drive. They rarely cause respiratory depression when used correctly.
- Psychological support and physiotherapy are very useful adjuncts to medications. However, these take time and if the patient is distressed, they are not helpful in the immediate cases (unless breathing techniques have been taught).
- **Benzodiazepines** are effective agents also, but usually **second line** after opioids.

Antiemetic

- In choosing an appropriate antiemetic it is important to consider first the underlying mechanism behind the nausea.
- Antiemetics each target slightly different receptors and have distinct modes of action making them applicable to certain clinical scenarios.
- **Metoclopramide** is a prokinetic, targeting the dopamine and serotonin receptors. It is useful in **delayed gastric emptying** and also **post-chemotherapy**.
- **Haloperidol** also hits the dopamine receptors and is most effective for **toxin** or **metabolic induced nausea**. And **opiate induced nausea**
- **Levomepromazine** is a very effective broad spectrum antiemetic as it antagonises the dopamine, serotonin, histamine and cholinergic receptors. It can, however, cause severe postural hypotension and sedation and is often reserved for use in terminal care.
- **Cyclizine** would be the most appropriate **first line agent** in case of **brain metastases**. It targets the dopamine and cholinergic receptors and is widely accepted as the best antiemetic for nausea associated with cerebral disease.
- **Dexamethasone** may be an appropriate management option in **brain metastases**, however in acute management of vomiting cyclizine would be a more appropriate first treatment.

lymphoedema associated with extensive pelvic disease

- Lymphoedema is a collection of excessive interstitial fluid which, in cancer patients, tends to be due to blockage of the lymphatic system by malignancy or fibrosis.
- Management tends to centre around manual lymphatic drainage, **multilayer lymphoedema bandaging** and skin care.
- Exercise can play an important part in encouraging lymphatic drainage, although specialist physiotherapy is rarely appropriate.
- Diuretics are unlikely to improve lymphoedema unless the swelling has significantly worsened following the prescription of a NSAID or corticosteroid, or if there is a cardiac or venous component.

Terminal agitation

- Patients often display 'terminal agitation' towards the end of life and this can be caused by several different triggers.
- One of these triggers is urinary retention which can even develop in patients who have not received any hydration for several days. Assessment for catheterisation should be one of the first management steps in a newly agitated patient.
- Once reversible causes for agitation have been excluded, medication can be a very important part of controlling this distressing symptom at the end of life.
- Midazolam is the drug suggested by the Liverpool Care Pathway (LCP) and this is most commonly used at a starting dose of 2.5 - 5 mg sc PRN.
- Haloperidol can be very effective in controlling hallucinations and confusion although benzodiazepines are traditionally the first line for terminal agitation.

Hypercalcaemia

- The most common life-threatening metabolic disorder associated with malignancy and should be treated as an oncological emergency.
- 10% of cancer patients develop hypercalcaemia, most of whom have disseminated disease and 80% die within a year.
- The cancers most frequently associated with hypercalcaemia are breast cancer, lung cancer, renal cell carcinoma and (most commonly) myeloma.
- There are three main mechanisms by which malignancy leads to hypercalcaemia:
 - 1) Osteolytic metastases with local release of **cytokines** (including osteoclast activating factors)
 - 2) Tumour secretion of **parathyroid hormone-related protein** (PTHrP) and
 - 3) Tumour production of **1,25-dihydroxyvitamin D** (calcitriol).

Treatment:

- ☒ Intravenous fluid rehydration followed by administration of a bisphosphonate (pamidronate).
- ☒ Osteonecrosis of the jaw is a well-recognised complication of bisphosphonate therapy, particularly intravenous agents.

Refeeding syndrome

- Artificial feeding is now commonly encountered within the field of palliative medicine, particularly given the speciality's expansion into neurodegenerative conditions.
- An awareness of refeeding syndrome is important as many of these patients will have experienced a period of reduced nutritional intake prior to PEG insertion, and will therefore be at risk.
- Refeeding syndrome occurs as a result of shifts in fluid and electrolytes in malnourished patients receiving artificial nutrition (either enterally or parenterally).
- The resulting biochemical upset can lead to cardiac arrhythmias, pulmonary oedema, seizures and death.
- Patients are usually monitored with regular blood tests to check for the characteristic picture of refeeding syndrome: **low potassium, magnesium and phosphate.**
- Sodium 136, potassium 2.5, magnesium 0.35, calcium 2.21, phosphate 0.25 is the correct answer as it shows the typical pattern of normal sodium and calcium with low potassium, magnesium and phosphate.

NICE guidelines on Nutrition support in adults (CG32) set out criteria for identifying patients at high risk of developing refeeding syndrome which included:

- BMI < 16 kg/m²,
- little or no nutritional intake for > 10 days and
- Unintentional weight loss greater than 15% within the last three to six months.

The Mental Capacity Act 2005 clearly sets out four conditions that have to be in place in order for a person to retain capacity to make decisions:

To understand the information relevant to the decision To retain that information To use or weigh that information as part of the process of making the decision, and To communicate his decision (whether by talking, using sign language or any other means).

In this case it would be his inability to communicate his decision that might interfere with his capacity. In such a case it is vitally important that all efforts are made to enable him to communicate, for example through drawing, typing, signing, etc, before the conclusion is reached that he lacks capacity: 'a person is not to be treated as unable to make a decision unless all practicable steps to help him to do so have been taken without success' (MCA, 2005).

Just because a patient is deaf does not mean that you cannot communicate information to them in an alternative way, therefore this would not necessarily interfere with his capacity.

Patients are entitled to change their mind about things, their decisions do not need to be reproducible over time, therefore his apparent change of attitude towards his illness does not interfere with his capacity.

Just because a patient makes a decision that does not agree with the advice of his doctor does not mean that he necessarily lacks capacity: 'a person is not to be treated as unable to make a decision merely because he makes an unwise decision' (MCA, 2005).

The MMSE is made up of a series of questions aimed at assessing a person's cognitive ability, for example those with a score of 22 might be classed as having signs of early dementia. Researchers have failed to demonstrate a reproducible link between MMSE score and presence (or not) of capacity. Therefore the option above which refers to MMSE score is incorrect.

Blood transfusion

- In palliative medicine the decision to offer blood transfusion is taken very much on an individual patient basis, without the existence of 'cut off values' or strict guidelines.
- The main reason for giving blood in the hospice setting is for symptom control.eg Disabling shortness of breath on minimal exertion
- These symptoms can range from fatigue, anorexia and dizziness to shortness of breath, headache and angina.
- Patients often develop anaemia chronically and, despite having very low haemoglobin levels, are relatively asymptomatic. In such cases transfusion is rarely given simply because a low haemoglobin is discovered.
- The presence of postural hypotension may or may not be an indication for transfusion. If the patient is complaining of dizziness or recurrent falls then this would more than likely become a case for transfusion, but if the patient remains asymptomatic then the discovery of a postural drop would not, in itself, trigger transfusion.
- If a patient suffers a major bleed then it is unlikely that blood transfusion would be appropriate. In the case of catastrophic haemorrhage the most important thing is to stay with the patient and not to leave them alone. If possible, administration of drugs such as midazolam and diamorphine can help to reduce the patient's awareness of the situation.
- Blood transfusion can play a very important role in symptom control and should not be discounted purely on the basis of a short prognosis.

Dexamethasone is notorious for causing compatibility problems and for this reason it is generally added last to syringe drivers in order to minimise the likelihood of precipitation.

Dexamethasone has a long half life which means it can usually be administered s/c once a day to circumvent miscibility problems.

Cyclizine is the other medication that can cause precipitation, particularly when used with higher doses of diamorphine. It is usually safer and more reliable either to use two separate syringe drivers or to choose an alternative antiemetic.

The combination of **diamorphine**, **midazolam** and **levomepromazine** is a common one, particularly since the advent of the Liverpool Care Pathway. There are no known miscibility problems with this combination.

Mebeverine is a commonly used antispasmodic, however it is only available in oral preparations

Hyoscine butylbromide (Buscopan) is an antispasmodic agent which can be given subcutaneously, which makes it an excellent choice of analgesic in bowel obstruction.

Carcinoid syndrome

- Carcinoid is a slow growing neuroendocrine tumour and symptoms of diarrhoea and flushes occur as a consequence of **metastases to the liver** and hence systemic release of vasoactive compounds such as **5-HT** and **bradykinin**.
- The best treatment for symptoms of carcinoid is the somatostatin analogue, **octreotide**, which improves symptoms and prognosis in carcinoid syndrome.
- If resistance or failure of octreotide: **hepatic artery embolisation**.
- In this case the treatment for the diarrhoea will be through treating the underlying diagnosis, which is carcinoid. Cyproheptadine is not a first line treatment for diarrhoea and in fact may cause diarrhoea as a side effect.

Carcinoid tumours

Carcinoid syndrome:

- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver

Features:

- flushing (often earliest symptom)
- diarrhoea
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation:

- 1) urinary 5-HIAA
- 2) plasma chromogranin A y

Management:

- somatostatin analogues e.g. octreotide

Mycosis fungoides

- Cutaneous T cell lymphoma
- The disease presents as a pruritic eczematous rash (the **pre-malignant** stage) and develops telangiectasias and areas of 'cigarette paper' atrophy.
- As malignancy develops, nodular lesions appear and proceed to become necrotic.
- **Mycosis fungoides** patch stage responds to **NBUVB**



GVHD

- multi-system disease. Organs usually involved in GVHD are skin, liver and gut.
- The rash on the palms and soles is classical.
- abnormal liver function tests (LFTs).
- There is also diarrhoea.

Transfusion associated GVHD

- a rare but usually fatal complication seen post BMT
- It is due to donor lymphocytes in transfused cellular components, for example, blood, platelets.
- These donor lymphocytes recognise the recipient as foreign, and as the recipient is immunocompromised due to the recent BMT they cannot set up a reaction to destroy these incoming lymphocytes.
- In this case the recipient is the host and the incoming lymphocytes are the graft.
- The lymphocytes cause acute **BM failure, liver dysfunction and GI symptoms**.
- There is no cure, only preventative measures, in that all cellular blood components given to BMT recipients need to be irradiated, this limits the functional activity of the lymphocytes.
- It usually occurs about 14 days after the affected transfusion.

Malignancy of unknown origin (MUO)

NICE guidance on [Metastatic malignant disease of unknown primary origin](#) recommends that

- If simple initial investigations fail to indicate a site for further investigation of **a malignancy of unknown origin (MUO)** then a CT chest, abdomen and pelvis should be attempted to elicit any suspicious areas which may be consistent with a primary malignancy.
 - Tumour markers are only useful in monitoring of disease response to treatment and should be interpreted with caution when the diagnosis is not known.
-
- Typhlitis or neutropenic colitis is a rare but serious complication of profound neutropenia which requires intravenous antibiotics.

Brain metastases

- The incidence of brain metastases is currently increasing due to better control of systemic disease and longer survival.
- Brain metastases usually originate from tumours via neoplastic emboli and therefore most often affect the 'watershed areas' at the end of the arterial supply.
- Lung cancer, melanoma and breast cancer are the primary tumours most frequently associated with metastatic spread to the brain,
- Melanoma usually causes multiple metastases whereas breast cancer tends to cause solitary lesions.
- The most common effect of a metastatic deposit is to cause oedema of the surrounding tissue leading to raised intracranial pressure and displacement, rather than infiltration, of the brain.
- Treatment of brain metastases is generally dictated by the type of cancer, the neurological status of the patient and the extent of systemic disease.
- General measures include high dose corticosteroids and palliation of any distressing symptoms such as agitation.

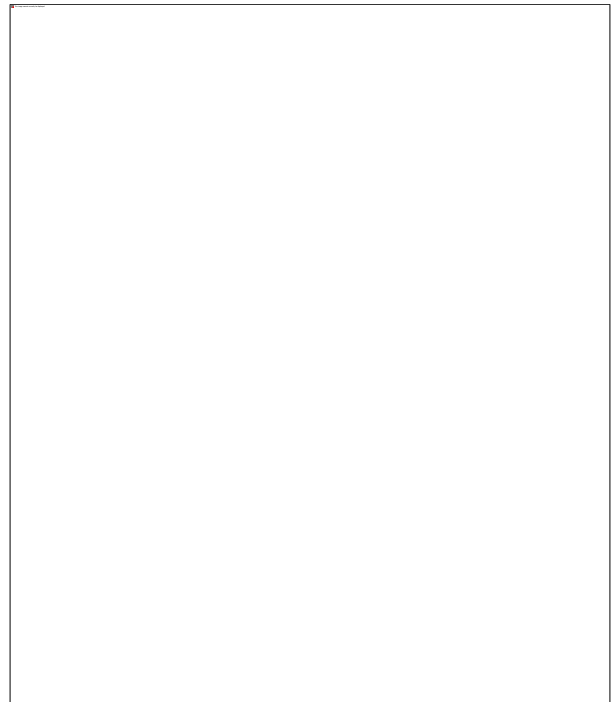


Image no 1) this patient has melanoma metastases that have cavitated

Image no 2) there are two slightly irregular ring-enhancing areas of low attenuation in the cerebellum consistent with metastases. Given the history of heavy smoking, the chest examination findings and hypercalcaemia, the suspicion of malignancy is high. The diagnosis is therefore cerebellar metastases, most likely from a squamous cell lung carcinoma.

=====

This gentleman is demonstrating classic signs of an acute dystonic reaction and given the history of starting a new medication in the last few days it would be important to exclude that as the cause.

Common presentations include protrusion of the tongue, trismus, facial grimacing, difficulty speaking, torticollis and oculogyric crisis. The patient's mental status and basic observations (for example, heart rate and blood pressure) remain unaffected. The most common drug causes of acute dystonia are neuroleptics (for example, haloperidol, levomepromazine), antiemetics (for example, metoclopramide) and antidepressants (for example, amitriptyline, trazodone).

Management is dominated by the need to stop the causative drug, followed by administration of either benztropine or diphenhydramine. Both of these medications block striatal cholinergic receptors which may help to balance cholinergic and dopaminergic activity and resolve the dystonia. Benzodiazepines may also be helpful.

Brain stem death

A code of practice for the diagnosis of brain stem death was published in March 1998 by a working party from the Royal College of Physicians ([A code of practice for the diagnosis of brain stem death](#)).

Brain stem death arises when there has been such devastating damage to the brain stem that it is no longer able to fulfil its function of cardiac and respiratory control. This inevitably means that the heart will soon stop beating. However, there can be a period of time when an individual is sustained by artificial ventilation and circulation despite the fact that they have already died.

Identification of this clinical scenario, accurate diagnosis of brain stem death and sensitive management of the patient's family, can lead to the humane withdrawal of artificial support and the avoidance of futile interventions.

Assessment involves the observation that all brain stem reflexes are absent (for example, corneal reflex) and this assessment must be carried out by two medical practitioners either together or separately. These practitioners must be registered for more than five years and at least one (but not both) must be a consultant.

Members of the transplant team are not permitted to be involved in the diagnosis of brain stem death.

The period of time between assessments is determined by clinical judgement although it must be sufficient to offer reassurance to all involved.

Death is pronounced after the second tests have been completed although the legal time of death is recorded as the time that the first set of tests revealed brain stem death

DVLA

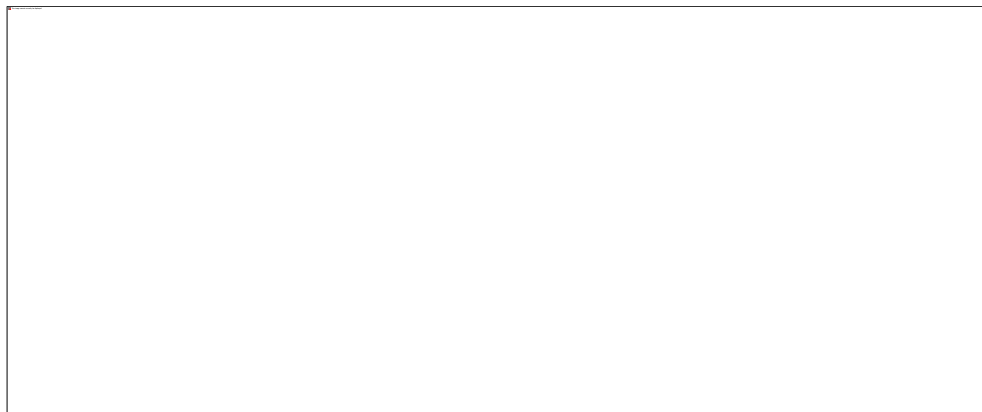
- Patients must inform the DVLA as soon as possible after receiving a diagnosis of a brain tumour, failure to do so may incur a fine of up to £1000.
- The period of disqualification differs according to the type of tumour and where it is in the brain.
- A patient with a high grade glioma (that is, WHO grade 3 or 4) such as a glioblastoma will be unable to drive for at least **two years** following completion of treatment. After the two years have elapsed the DVLA will consult with the physicians involved in the patient's care and a decision is made regarding return of the licence.
- A patient with a **solitary metastatic deposit** that is fully excised would be considered for a licence **one year** after primary treatment if free from recurrence and no evidence of secondary spread elsewhere.
- Those with **multiple metastases** would require at least **two years** off driving from time of completion of treatment. After the two years have elapsed the DVLA will consult with the physicians involved in the patient's care and a decision is made regarding return of the licence.
- **A first unprovoked seizure** requires **six months** off driving from the date of the seizure unless there are factors which suggest an unacceptably high risk (>20% per annum) of a further seizure.
- For a patient with **known epilepsy** who has a **seizure whilst awake**, they must have their licence refused or revoked for **one year**.



The diagnosis is a massive fibroid.

The bladder is inferior to the large midline mass arising out of the pelvis. There are separate planes of cleavage from the bladder and the anterior abdominal wall, which have normal appearances.

This mass is contiguous with the uterus as it wraps around the bladder.



Metastasis

There is a soft tissue mass destroying a large portion of the scapula